Melrose I teaches the formation of poly(2-propenal, 2-propenoic acid) from acrolein homopolymers, as well as acrolein copolymers, and their use to treat or prevent gastrointestinal disease in various animals. Melrose I merely describes how to form the starting material that can be used to form the polymeric antimicrobial which is administered in accordance with claim 49.

Melrose II is directed to overcoming the problem of poly(2-propenal, 2-propenoic acid) instability in aqueous solutions. Specifically, Melrose II teaches the formation of a stabilized formulation of poly(2-propenal, 2-propenoic acid), using phenols and anionic surfactants, to form an emulsion that includes the poly(2-propenal, 2-propenoic acid) is a hydrophobic phase.

Neither Melrose I nor Melrose II teaches or describes the formation of what is described in the present application as a super-activated form of poly(2-propenal, 2-propenoic acid), which is formed by the process of heating poly(2-propenal, 2-propenoic acid) comprising from 0.1 to 5 moles of carboxyl groups per kilogram of polymer in a polyalkylene glycol in the presence of water at a temperature in the range from 40°C to 150°C for a period from 1 to 1400 hours. Consequently, neither of Melrose I nor Melrose II describe the use of this super-activated form of poly(2-propenal, 2-propenoic acid) for treating gastrointestinal disease as recited in claim 49 and claims dependent thereon.

In addition to the foregoing, applicants respectfully submit that the basis asserted for the obviousness rejection is flawed and, moreover, the present application demonstrates in the examples that the claimed invention involves an unexpected improvement in anti-microbial activity. These two issues will be addressed separately below.

At page 5 of the office action, the U.S. Patent and Trademark Office ("PTO") acknowledges that Melrose I does "not teach the instant claimed method of heating the poly(2-propenal, 2-propenoic acid) in the presence of polyethylene glycol." The PTO relies on Melrose II for the proposition that one of ordinary skill would be motivated to optimize the time for heating in polyethylene glycol in Example 8 within the range of 1 to 1400 hours.

Applicants submit that reliance on Melrose II in this manner is improper and without basis. There is nothing in Melrose I or Melrose II which would motivate a skilled person to modify the heating time, because—without the benefit of hindsight—heating for purposes of dissolving ingredients in solution would be *minimized* rather than extended in the manner as recited in claim 49.

As noted above, Melrose II is directed to overcoming the problem of poly(2-propenal, 2-propenoic acid) instability in aqueous solutions. In particular, Melrose II recites at page 6, lines 9 to 19:

> It has now been found that whilst basic aqueous compositions containing the poly(2-propenal, 2-propenoic acid) are biostatic and/or biocidal; nevertheless, the compositions are appreciably unstable. Although, it has further been shown that lowering the pH (lowering the hydroxyl ion concentration) of such compositions/solutions increases their chemical stability, counter-productively, it has been found that acidification of the composition to pH's below approximately pH 6, causes precipitation of the poly(2-propenal, 2-propenoic acid).
>
> It has now been shown that this precipitation can be avoided until approximately pH to 3.5 (ie. over ten-fold, less hydroxyl ion concentration), by a method of formulating in which the poly(2-propenal, 2-propenoic acid) is first dissolved in dilute aqueous base, then anionic surfactant added, before the acidification.

The use of other organic compounds such as phenol, EDTA isothiazolinones and glutaraldehyde in the process is also discussed. Melrose II recites at page 8, lines 16 to 20:

> It has now been shown, further, that not only is the antimicrobial activity increased but surprisingly, it is *synergistically* increased by incorporating in the compositions containing the poly(2-propenal, 2-propenoic acid) either, EDTA (and/or its salts), and/or phenols, and/or isothiazolinones, and/or glutaraldehyde; see Example 7 hereinafter.

However, none of these additional compounds or classes includes polyethylene glycol.

Example 8, which is relied on by the PTO, examines a model for examining migration of various agents across the skin. The base used for composition is polyethylene glycol 1000. Polyethylene glycol 1000 is a softening agent used in cosmetics and, hence, a good choice of solvent for observing skin penetration. In the preparation of the composition, poly(2-propenal, 2-propenoic acid) is dissolved in polyethylene glycol 1000 by stirring at 70°C for 2 minutes. Other ingredients, including 10g sunscreen agents, emulsifier PEMULIN TR1 and emulsifier CARBOPOL 2984, are added while maintaining the temperature at 70°C for 15 minutes.

The purpose for heating the composition is simply to dissolve the various components. After all, if the components were not completely dissolved, then it would not be possible to assess their migration across the model for skin because undissolved solids would be unable to migrate. Heating is clearly carried out for this purpose, and nowhere is it suggested that heating would be useful for any purpose other than dissolving components. (Indeed, no other reference is made to heating the polymer in air to form poly(2-propenal, 2-propenoic acid) from polyacrolein.)

Thus, Melrose II makes no suggestion that heating in any solution, let alone polyethylene glycol, should be performed for any purpose other than to dissolve components. Consistent with this purpose, heating is conducted for a short time (approximately 17 minutes) to provide a liquid composition for dissolution of various solids, including 0.5g poly(2-propenal, 2-propenoic acid), 10g sunscreen and 0.5g emulsifiers in 10g of polyethylene glycol 1000.

Accordingly, in asserting that the extension of the heating time to from 1 to 1000 hours is mere optimization, the PTO's position assumes knowledge that heating is for a purpose other than dissolution of the components—namely, to afford the super-activation as described in the present application. This information, *first disclosed in the present application*, is nowhere to be found in the prior art. If one of ordinary skill in the art were to optimize the dissolution process, such optimization would merely call for the minimum time required to dissolve the components in order to avoid the energy cost and deterioration normally associated with unnecessary heating. If optimization were the goal, therefore, then a person of ordinary skill in the art would have looked for ways to reduce the heating time and temperature to achieve the desired dissolution of ingredients. Thus, one of ordinary skill in the art would have been guided *away* from the process limitations recited in claim 49.

Indeed, *a priori*, one of ordinary skill in the art would have expected that extended heating would accelerate aging of the active components and the loss of antimicrobial activity. This is explained in the present application at page 20, lines 1-13. The aging tests, at increased temperature and for various durations, were expected to result in the loss of stability and the loss of antimicrobial activity. It was during these tests that the applicants recognized the surprising improvement in activity provided by heating in polyethylene glycol for an extended period. The aging tests, intended to accelerate the loss of antimicrobial activity, actually produced the *opposite* effect. As explained in the present application, this result was unexpected.

From the foregoing, it should be appreciated that none of the cited art provides any suggestion to prepare the super-activated form of poly(2-propenal, 2-propenoic acid) by the process of heating poly(2-propenal, 2-propenoic acid) comprising from 0.1 to 5 moles of carboxyl groups per kilogram of polymer in a polyalkylene glycol in the presence of water at a temperature in the range from 40°C to 150°C for a period from 1 to 1400 hours, let alone any expectation that such heating under these conditions would achieve the improvement in activity as described in the present application. For these reasons, the presently recited invention would not have been obvious to a person of ordinary skill in the art, and the PTO has failed to establish *prima facie* obviousness.

Moreover, the Examples of the present application unambiguously demonstrate the significant improvement provided by heating in polyethylene glycol for a period of 1 to 1400 hours. For instance, Example 8 shows that the kill time is dramatically reduced when the composition is heated for extended periods of 1 to 1400 hours. Applicants would also like to draw the attention of the PTO to Examples 20 and 21 of applicants' co-pending PCT application WO 2003/061672 (copy attached as Exhibit 1 to the submission dated September 15, 2008), which demonstrate the difference between the derivative whose use is recited in claim 49 and the prior art poly(2-propenal, 2-propenoic acid). In comparative Example 20(a), poly(2-propenal, 2-propenoic acid) is formed in accordance with the prior art approach (oxidation in air). In Example 20(b), the polymer is super-activated by reaction with polyalkylene glycol (specifically polyethylene glycol) at 100°C for four hours. Example 21 specifically studies the activity of the two compositions against gastrointestinal disease (cancer cells). The composition of Example 20(b), whose use is recited in claim 49 of the present application, exhibits a significantly improved activity when compared with the prior art poly(2-propenal, 2-propenoic acid).

In aggregate, the examples of the present application and the examples of WO 2003/061672 demonstrate that a difference in kind exists between prior art poly(2-propenal, 2-propenoic acid) and the super-activated form prepared in the manner recited in claim 49. Because the recited product *per se* is different from prior art poly(2-propenal, 2-propenoic acid) (*see* Table of NMR data on page 25 of application) and possesses an unexpected improvement in its activity, the use thereof in accordance with claim 49 certainly would not have been expected.

For all these reasons, the rejection of claims 7, 9-13, 15-17, 25-28, 30-39, 42, 46, 47, and 49 for obviousness over Melrose I and Melrose II is improper and should be withdrawn.

The rejection of claim 29 under 35 U.S.C. § 103(a) for obviousness over Melrose I and Melrose II, further in view of U.S. Patent Application Publ. No. 2002/0127207 to Harris et al. ("Harris") is respectfully traversed.

The PTO cites to Harris at page 6 of the office action for teaching the treatment of livestock with antibacterial compounds, for treatment of *E. coli* infections and diarrhea in pigs. However, the PTO has failed to demonstrate how Harris overcomes the above-noted deficiencies of Melrose I and Melrose II with respect to claim 49, upon with claim 29 depends. Therefore, the rejection of claim 29 for obviousness over the combination of Melrose I, Melrose II, and Harris is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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